IMMUNITY IN SYPHILIS*

BY

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There are those who view the study of immunity in syphilis and the development of an effective immunizing agent as problems of academic interest only since the advent of penicillin therapy. There are also those who believe, particularly since the world-wide resurgence of syphilis occurring after 1957, that therapeutic and case-finding advances such as have occurred with syphilis represent only holding actions until successful immunization can be accomplished. From the standpoint that the most certain evidence of complete elimination of acute syphilis is the development of a definite re-infection, penicillin has been shown to effect, as easily to-day as 20 years ago, a dramatic cure. In fact, the cycle of cure, re-infection, cure, re-infection, etc., occurs so frequently in given individuals that the term "ping-pong" syphilis (Schoch and Alexander, 1943) was coined to describe this frequent clinical observation.

With the development of a repository form of penicillin permitting adequate "one shot" treatment of infections, it was envisaged that syphilis morbidity would soon reach an irreducible minimum, which would be maintained, and syphilis would no longer be a public health problem. It appeared for several years that this was true. However, since 1957 there has been a national and international resurgence of syphilis morbidity, and the reasons for this occurrence are not understood.

It is axiomatic that the successful control or eradication of a communicable disease may be effected wherever it is possible to immunize the host effectively or to eliminate the vector. As long as effective immunization cannot be accomplished, the present control methods and techniques must, of necessity, be extended and more vigorously applied against syphilis. However, the concept of control by applied immunology has within it the philosophy that the final solution of the problem will be attain-

able only when successful immunization can be accomplished. It is not hopeful that this can be accomplished unless more research facilities, funds, and talents can be applied to provide an intensified programme dedicated to the cultivation of virulent *Treponema pallidum* and the use of the organism, or products thereof, to produce resistance to infection.

The purpose of this paper is to present a unified collection of current knowledge of clinical and experimental syphilis in relation to resistance to infection and to stimulate interest in the problem, as well as an awareness of the importance of the immunological concept in the control of syphilis. Papers of a similar nature which were relatively complete at the time of their publication are those of Neisser (1911), Chesney (1927), Urbach and Beerman (1947), and Magnuson (1948).

Before entering into the presentation of the observations and data pertaining to resistance to syphilitic infection, it might be well to point out some of the peculiarities of syphilis that are not encountered in other infectious diseases. The problems and peculiarities of syphilis appear to some to set it apart from other infectious diseases. To those unfamiliar with the literature, it should be pointed out that the subject is fraught with numerous divergencies of opinion and interpretations of experimental data. There are those who are convinced that true immunity in syphilis does not exist, and there are others who are equally convinced that immunity does occur in certain circumstances. Further, some investigators feel that the inability to produce infection upon challenge with virulent organisms is merely a demonstration that the original infection was not eliminated and is not therefore a demonstration of increased resistance to the organism. Proponents of the view that immunity does not result from previous infection(s) cite the irrefutable observation of "ping-pong" syphilis and the recrudescence of clinical manifestations of the

organism in late syphilis. The implication here is that the patient has not developed resistance or immunity, which is usually seen in other infectious diseases, to the organism he harbours. There are other peculiarities about the immunology of syphilis, but these examples should be sufficient to make those unfamiliar with the literature and the subject aware that many basic problems remain unsolved.

Among them, the development of resistance, the maintenance of resistance if it occurs, and the degree in which it may be important in the prevention or acquisition of the disease have been subjects of considerable speculation which are obviously in need of definitive experimentation.

NATURAL IMMUNITY IN MAN

It is generally considered that man does not possess any significant resistance or immunity to syphilitic infection. It has been agreed that man's principal defence against syphilitic infection has been the maintenance of an intact skin and mucous membrane barrier, since effective natural humoural or tissue resistance has not been demonstrated. It is probable that intact skin and, to a lesser extent, intact mucous membrane do provide a barrier to syphilitic infection in man, but the degree of protection is indeterminate. Mahoney and Bryant (1933) reported that male rabbits may be infected by exposing the normal mucous membrane of the prepuce to a treponemal suspension, and they interpreted this to mean that infection could take place by penetration of the organisms through an intact mucous membrane. The observations of von Werssowetz (1948) that approximately 50 per cent. of contacts of primary and secondary syphilis do not become infected is difficult to evaluate in terms of natural resistance. The inter-related factors of degree and duration of contact, numbers of organisms present at the contact site, relative virulence of the organisms, and the roles of physical and systemic factors are impossible to evaluate, either individually or collectively, in relation to the measurement of natural immunity in man.

Magnuson, Thomas, Olansky, Kaplan, de Mello, and Cutler (1956) have published the only report of a controlled experiment involving human volunteers and graded doses of virulent (Nichols strain) *Treponema pallidum*. In that study eight volunteers were injected intracutaneously in four sites on the forearm with doses of 10, 100, 1,000, and 10,000 organisms. All patients developed dark-field positive lesions during the observation period which was terminated either by treatment or the development of secondary lesions. Using the Bliss (1935) dose-response technique, the 50 per cent. infectious dose

was calculated to be 57 organisms. The same suspension of organisms injected into rabbits at the same dosage level and time gave a calculated 50 per cent. infectious dose of 23 organisms. It was concluded from this study that the 50 per cent. infectious dose of the Nichols strain is approximately the same for man and rabbit. It is of interest, in relation to the natural immunity and response to infection of the eight volunteers, that as the size of the inoculum increased the incubation period tended to become shorter and that the larger inocula produced larger and more ulcerative lesions than did the small inocula. If it is assumed that each of the inoculated organisms survived and gave rise to two, etc., then at this period during the primary infection it is tempting to postulate that the tissue responses were the result of the metabolic products and/or soluble surface antigens of the organisms rather than the result of somatic substances resulting from dissolution of the organisms. Further, in this regard, organisms killed by such a mild measure as lyophilization do not give rise to tissue responses that are observed when the organisms are metabolizing within the tissues.

There are no published reports of controlled experiments to demonstrate natural immunity differences between sexes and races. Epidemiological studies suggest that there are differences in the course of the disease and in clinical manifestations, but how many of these variations are associated with immunity phenomena and how much with environmental and physiological factors is not known.

There are no data to substantiate the supposition that man may have, in some instances, sufficient natural immunity or resistance to overcome the initial invasion of treponemes and develop an asymptomatic infection. There are conflicting data in the literature concerning the development of asymptomatic syphilis in the rabbit. Morgan (1941) and his co-workers reported that infections resulting from the injection of a few organisms frequently resulted in asymptomatic infections, and that greater numbers regularly resulted in symptomatic infections. Bessemans (1934) reported that approximately 10 per cent. of rabbits receiving the usual inoculum developed asymptomatic infection. Rake, Dunham, and Donovick (1947) found very few instances of asymptomatic infection, an observation supported by Magnuson, Eagle, and Fleischman (1948). The latter found that one treponeme injected intra-testicularly would produce a symptomatic infection and that five organisms injected intracutaneously would produce infection in 50 per cent. of the animals. Magnuson and his co-workers considered the possibility of differences of strain

adaptation and of rigid control of environmental conditions, such as temperature, to be responsible for the discrepant observations. Thus, the effects of strains and environmental factors on the development of asymptomatic infections in man are unknown, and the fact that a similar low incidence of asymptomatic infection results from these factors cannot at present be explained.

NATURAL IMMUNITY IN LOWER ANIMALS

There is general agreement that apes, some species of monkeys, and rabbits are the only animals which may be regularly infected experimentally and develop the acute disease that is similar to that seen in man. However, these animals, as far as it is known to date, do not respond to the disease with the development of late manifestations of the cardiovascular and central nervous system as observed in man.

Attempts have been made to produce the disease in guinea-pigs, white rats, brown or wharf rats, white mice, grey mice, rellmice, dormice, coypu, squirrels, gophers, marmots, ferrets, hamsters, hedgehogs, dogs, foxes, pigs, calves, sheep, goats, deer, cats, frogs, canaries, hens, roosters, and pigeons. It was agreed one time that none of the above was susceptible to infection with strains of treponemes known to have been infectious for rabbits, and therefore that they had an absolute natural immunity to syphilis. It is now known that certain of these animals may be infected and develop darkfield-positive lesions at the inoculation sites or asymptomatic infections demonstrated by the transfer of tissues to the rabbit with resultant darkfield-positive lesions.

Asymptomatic infections were demonstrated in the mouse and rat by Kolle and Schlossberger (1926), in the hamster by Hu and Pearce (1932), and in the rellmouse and coypu by Jahnel (1937). The mechanisms which provide resistance in certain species to the point of resisting symptomatic disease, but are insufficient to prevent an asymptomatic infection are not known.

Numerous attempts to infect cats by intratesticular inoculations have generally met with failure. However, Levaditi and Yamanouchi (1908) demonstrated that cats could be infected if inoculated intraocularly. This was confirmed by Wagner (1936)

Lesinski, Wicher, Zajac, and Jakubowski (1960) reported the successful infection of guinea-pigs with the Nichols strain. Intradermal inoculation in the scrotum produced characteristic lesions.

ACQUIRED IMMUNITY

Historically, the subject of acquired immunity to syphilis has had two groups of proponents. One group insists that immunity, or resistance to re-infection, persists only as long as the patient maintains the infection. This has been designated "infection immunity" as well as "chancre immunity". The scientist generally considered to be the principal proponent of this view was Neisser (1911). Part of the evidence on which the principle of "chancre immunity" was based was the well-established fact that, if a lesion was auto-inocuable, it was a "soft chancre" and, if it was not auto-inocuable, it was a "hard chancre". It was also well-established that, if the patient was adequately treated, the "chancre immunity" was lost. This was evidenced by numerous instances in which adequately-treated patients developed new primary lesions, whereas, inadequately-treated or untreated patients did not develop new primary lesions. Among the reports on this concept of acquired immunity to syphilis are those of Neisser (1911), Finger and Landsteiner (1912), Kolle and Prigge (1934), and Truffi (1930).

The views of Neisser and his followers were not challenged seriously until Chesney (1927) set forth the principles which present evidence seems to support in regard to the development of resistance to re-infection. Chesney used his own data and the data of those who held to the view of "chancre immunity", and came to the conclusion that resistance to re-infection developed in relation to the duration of the disease and its termination by adequate treatment. Chesney's experimental data, and those of others available to him, led him to the conclusion that if the primary or immunizing infection lasted less than 3 months, subsequent challenge with the homologous strain resulted in clinical re-infection. However, if the primary or immunizing infection were allowed to persist for 3 months or longer before termination by adequate treatment, a subsequent challenge with the homologous strain did not usually result in a symptomatic re-infection. Among the older reports on this concept of acquired immunity to syphilis are those of Chesney and Kemp (1926), Turner (1939), Uhlenhuth and Grossman (1928), Gastinel (1945), Vásárhelyi (1936), Worms (1942), Breinl and Wagner (1929), Brown (1930), Manteufel and Herzberg (1933), and Matsumoto (1930).

Contemporaries of the older workers and reviewers have tended to negate some of the conclusions regarding attempts to produce re-infections in apparently immune animals on the basis that arsphenamines were used which were not totally eliminated from the host at the time of challenge.

Since the advent of penicillin in the treatment of syphilis, there have been several studies of experimental syphilis in which it appears unlikely that residual penicillin could be responsible for the prevention of re-infection upon challenge with the homologous strain.

It appears that the first experimental data concerning acquired immunity in syphilis in which penicillin was used to terminate the infection were those of Gastinel, Collart, and Mollinedo (1945). This report, which involved both arsphenamine and penicillin therapy, demonstrated that rabbits which were infected for 6 months before treatment with penicillin were completely resistant to re-inoculation.

Arnold, Mahoney, and Cutler (1947a, b) made two reports on the development of resistance to re-infection in which penicillin was used to terminate the immunizing infection.

In the first report, 37 rabbits were treated with curative amounts of sodium penicillin after 6 to 8 weeks of infection. Challenge was made 10 days after cessation of therapy with the homologous strain (Nichols). The initial infections and challenge were made by subscrotal injections. Ten of the animals (27 per cent.) developed dark-field-positive lesions at the challenge site, and the other 27 (73 per cent.) were followed for 4 months without evidence of re-infection. However, all were found to have asymptomatic infections which were demonstrated by positive lymph-node transfers to normal rabbits at the end of the 4-month observation period.

In the second paper, a companion study was made in which the duration of the primary infection was 8 months. When challenge was made 10 days after completion of penicillin therapy and in the same manner as the preceding paper, it was found that none of the animals developed lesions at the inoculation sites; 18 (53 per cent.) developed asymptomatic infections and the remaining sixteen (47 per cent.) were not re-infected. In this study, inguinal and popliteal lymph nodes were transferred to normal rabbits and observed for 100 days to determine the presence or absence of asymptomatic infection. It is apparent that a moderate immunity existed in the animals after 8 weeks of infection (73 per cent. asymptomatic re-infections) and that a more solid immunity developed after 8 months of infection (47 per cent. not re-infected; 53 per cent. asymptomatic infections).

Those who hold the view that resistance to re-infection is related to the duration of the immunizing infection generally agree that resistance is seldom, if ever, absolute. That is, if a sufficiently large number of organisms is used for the challenge, the resistance of an animal may be overcome and either a symptomatic or an asymptomatic re-infection will result. Magnuson and others (1948) have shown that the infectious inoculum of the Nichols strain in normal rabbits is extraordinarily small. Magnuson

and Rosenau (1948) are of the opinion that most of the studies of immunity in experimental syphilis have used challenge inocula many times greater than that of the minimal infectious inoculum and that high degrees of resistance were required to demonstrate any immunity. Magnuson and Rosenau (1948) were the first to employ precise numbers of organisms and quantitative measurement of the rate of development and the degree of acquired immunity by use of carefully-graded challenge inocula. Employing the concept of carefully-graded inocula, Magnuson and Rosenau (1948) reported observations made with 263 rabbits divided into groups, in which the immunizing infections were of 3, 6, 12, and 24 weeks, duration. The animals were treated with either mapharsen or penicillin and were challenged 6 weeks after treatment with carefully-graded inocula of the homologous (Nichols) strain of *T. pallidum*. Challenges made in this manner resulted in symptomatic re-infection (dark-field-positive lesion at site of challenge), asymptomatic re-infection (no lesion at inoculation site but node transfer positive), or immunity (no lesions and node transfer negative). Using the quantitative technique, it was demonstrated that partial immunity was established after as little as 3 weeks of infection and that the immunity was progressive in degree during the 24-week observation period. Increased resistance to re-infection was determined by the progressive increment in the number of organisms required to produce a given response at the time of challenge. Magnuson and Rosenau (1948) summarized:

"Starting from a small, but demonstrable, immunity at 3 weeks, the immunity increased to such a degree that by the 24th week animals were partially protected (asymptomatic re-infection) against 10^8 minimal infectious inocula. 200,000 minimal infectious inocula were required to produce symptomatic re-infection in 50 per cent. of these animals and immunity in the remainder".

In the introduction to this paper, it was pointed out that there are numerous instances in which divergencies of opinion and interpretations of experimental data exist in studies of experimental syphilis. Turner and Hollander (1957) were of the opinion that re-infection in syphilis was primarily determined by the immune status of the host and therefore that re-infection was not materially influenced by the number of organisms employed in the challenge inoculum. Turner cited reports of Magnuson and Rosenau (1948), Magnuson, Rosenau, and Clark (1949), McLeod and Magnuson (1955), and Magnuson, Thompson, and Rosenau (1950), in which he considered the data of each paper as supporting evidence for his opinion that re-infection

occurs largely independently of the size of the challenge inoculum.

Some of the older clinicians and investigators were of the opinion that a few early lesions did not give the protection against late sequelae of the disease compared to the protection which developed as a result of extensive early lesions. Brown and Pearce (1921) expressed this concept in their "Law of Inverse Proportions"—the more intense the early lesions, the less intense were late manifestations of the disease. More recent investigations of the relationship of antigenic mass to the development of immunity are those of Turner and Nelson (1950), Hollander, Turner, and Nell (1952), and Magnuson, Thompson, and Rosenau (1950).

Turner and Nelson (1950) inoculated three groups of rabbits with 500, 50,000, and 25,000,000 organisms in the testes and, on the 28th post-inoculation day, all animals were given curative amounts of penicillin. One week after the last injection of penicillin, all animals and controls were challenged intracutaneously on the back with approximately 500 organisms at each of four sites. In this experiment all three groups of animals had been infected for the same length of time, but the duration of detectable lesions varied between the three groups which affected the development of resistance to re-infection. The group that had been infected with the fewest organisms (500) had lesions for only 3 days at the time treatment was begun and, upon challenge, showed little enhanced resistance to the challenge. The group that received the largest infecting inoculum (25,000,000) had had lesions for 20 days and showed a high degree of immunity to the challenge inoculum.

The report of Hollander and others (1952) also demonstrated that the presence of small numbers of organisms over a rather prolonged time did not lead to immunity. In that study the incubation period was prolonged by the judicious use of small amounts of penicillin. After 20 weeks of subclinical infection, the withdrawal of penicillin resulted in an evolution of the syphilitic disease process which was essentially that which might have been expected from a fresh infection. Neither Wassermann nor treponemal immobilizing antibodies developed during the prolonged period of subclinical infection.

Magnuson and others (1950) maintained rabbits with low levels of antigenic mass by allowing the primary lesions to appear and giving subcurative amounts of penicillin at 3, 6, and 9 weeks and adequate penicillin treatment at 12 weeks. The purpose of the investigation was to determine if treated but uncured infections could produce demonstrable degrees of immunity. It was concluded that during subcurative infection additional acquired immunity may develop, but the rate of development of immunity was estimated to be only one-sixth that of the untreated infection.

Most of the investigations of the development of immunity in syphilis have used the same strain for initiating the infection and for challenge. All of the older reports indicate that partial immunity develops against heterologous strains but that it is of much lesser degree than that which is demonstrated with the homologous strain. If one subscribes to the theses of Magnuson and Rosenau (1948) that differences in immunity are masked by the use of overwhelmingly large inocula and that quantitated inocula are capable of demonstrating degrees of immunity, it is obvious that the problems of immunity to heterologous strains requires re-investigation within these concepts.

The report by Worms (1942) is significant in that four strains were used. In that study, an attempt was made to demonstrate pan-immunity by using three strains to develop the immunizing infection. A fourth strain was used for subsequent challenge which did not result in infection. This study is of interest in relation to the practical immunization against syphilis. If it should be established that immunity in syphilis is largely strain-specific, it appears that a mixture of several representative strains might be used to develop a true pan-immunity.

There are few reports concerning the duration of immunity in experimental syphilis in rabbits. Magnuson and others (1949) immunized rabbits with an infection of 12 weeks which was terminated by penicillin therapy. Quantitative challenges made with the homologous (Nichols) strain at 6, 12, 24, and 48 weeks did not demonstrate a diminution of immunity with time. Gastinel, Pulvenis, and Collart (1938) found that, of nine rabbits challenged from 10 to 20 months after treatment, three developed symptomatic re-infection compared with only one of twenty animals challenged during the first 10 months after treatment. These data suggest that there may be a reduction in degree of immunity with time. A similar study by Arnold, Wright, and McLeod (1950), in which the immunizing infection was of 8 months' duration and challenges were made for periods of 6 to 28 months after adequate penicillin therapy, indicated that the immunity established in latent syphilis in rabbits (8 months' duration) persisted during the 28 months of post-treatment observation and challenge. It is obvious that more studies are needed to clarify the problem of the persistence of immunity after varying duration of immunizing infections.

It has been suspected by certain workers that the infallibility assigned to lymph node transfers for the determination of the persistence of infection or therapeutic cure in experimental syphilis was questionable. In experimental yaws in rabbits, McLeod and Magnuson (1952) found that a high proportion of untreated cases failed to give positive results on transfer of lymph nodes to normal rabbits. In contrast to yaws, the reliability of lymph-node transfers in studies of early experimental syphilis in rabbits is generally thought to be relatively high. However, in late syphilis, reports by Collart, Borel, and Durel (1962a, b, c) indicate that treponemes may persist in lymph nodes after what is generally considered to be adequate, and even after massive, penicillin therapy.

The English summary of the first paper (1962a) is as follows:

"Rabbits were inoculated with *T. pallidum* (Nichols strain) and 2 years later treated with benzathine penicillin. After about one year, the smears of their popliteal lymph nodes stained with a silver-staining technique (described in the paper) showed the presence of more or less typical *T. pallidum*. However, the transfer of these nodes did not induce any lesion in receptor rabbits; in these rabbits, the immobilization test remained negative with one exception.

"It should be pointed out that typical late lesions appeared after the administration of cortisone in one of the treated animals".

In the second report by Collart, Borel, and Durel (1962b), concerned with late syphilis in man, it was found that nine patients with syphilis of several year's duration harboured treponemes in their inguinal lymph nodes. Six of the patients were said to have had intensive treatment. Part of the nodes of four cases were injected into rabbits. One case was too recent to report on, but lesions developed in the other three after a prolonged incubation period. In two cases the fluid obtained by puncture contained typical treponemes, yet the lesions "rapidly stopped short". The authors commented that the treponemes of these patients had retained their vitality, but concluded that they had lost all or part of their virulence and had become commensal microorganisms. The authors suggested that the organisms might in certain biological conditions revert to the virulent state, but pointed out that they did not have data for or against such an occurrence.

The third paper by Collart, Borel, and Durel (1962c) concerns massive treatment with penicillin to eradicate the infection. Of thirteen rabbits treated with massive doses of penicillin, seven survived for from 17 days to 9 months after the end of treatment. Silver-stained preparations from the lymph nodes of these animals showed typical treponemes on six occasions and atypical forms on one occasion. The primary infection of these animals was of 22 months' duration.

In all three of these papers by Collart and his co-workers, it is pointed out that immobilizing antibodies were demonstrable in their late well-treated cases. They suggest that the persistence of organisms in the tissues provides the antigenic stimulus which maintains the immobilizing antibodies. The authors did not speculate (though one is tempted to do so) that immobilizing antibodies may become a true indicator of either active or latent syphilis if subsequent studies demonstrate that negative node stains are positively correlated to the absence of immobilizing antibodies.

Many workers are quite dubious about the identification of treponemes by silver-impregnation techniques. It is felt that certain tissues, fibrin, etc., may produce artefacts that simulate the morphology of the treponeme. In this regard it is apparent that the work of Collart and co-workers would be considerably strengthened if they had employed the more specific fluorescent antibody techniques adapted to tissue.

CROSS-IMMUNITY

Historically, clinicans having experience of both syphilis and yaws have generally been of the opinion that infection with either of these diseases protects against infection with the other. Studies of an epidemiological nature, such as those of Parham (1922) and Butler (1922), suggest that in areas where yaws is widely prevalent there is little syphilis, the inference being that yaws in childhood protects the adult against syphilis. In the older literature, studies such as that of Jahnel and Lange (1925) indicated that *bona fide* syphilis protected against challenge with yaws organisms. Four paretics were challenged with yaws organisms that had been propagated in rabbit testes. Challenges were made by rubbing yaws-infected tissues into the scarified skin, and by intracutaneous, and subcutaneous implantations of tissue. None of the four patients developed lesions, whereas a normal individual used as a control developed typical yaws lesions. Data and discussion of the older experimental literature pertaining to cross-immunity between syphilis and yaws in monkeys and rabbits can be found in the work of Chesney (1927), and those of more recent studies can be found in that of Turner and Hollander (1957).

Experimental data concerning cross-immunity among the treponemal infections have not resulted in unequivocal conclusions. Studies reported by Turner, McLeod, and Updyke (1947) and by McLeod and Magnuson (1955) may be cited as examples of similar studies with different conclusions. In both studies the same strains of yaws and syphilis were used, and Dutch rabbits were infected intra-

testicularly and challenged intracutaneously. In the study by Turner, McLeod, and Updyke (1947), rabbits with immunizing yaws infections of 6 months' duration did not develop symptomatic syphilitic infection when challenged with 2,000,000 syphilis treponemes. In the study by McLeod and Magnuson (1955), in which the immunizing infection was of 7 to 9 months' duration, challenge with 100 of the same strain of syphilis treponemes resulted in symptomatic infections. The only essential difference in these studies was that the animals in the Turner, McLeod, and Updyke study were untreated and those in the McLeod and Magnuson study were treated with penicillin before challenge. McLeod and Magnuson were of the opinion that the effect of curative therapy abolished or greatly reduced the protection which latent yaws infection affords against symptomatic re-infection with syphilis. However, interpretation of the data in this manner is complicated by the fact that treatment did not reduce protection when syphilis rabbits and yaws rabbits in the study were challenged with their homologous strains without the development of symptomatic re-infections.

Of particular interest are the four experiments reported by Turner and Hollander (1957) with syphilis, yaws, and *Treponema cuniculi* strains.

In the first experiment, three groups of twenty rabbits were infected with a syphilis strain, a yaws strain, and a *cuniculi* strain. A fourth group of twenty rabbits was maintained uninfected under the same laboratory conditions as controls. After 6 months of infection, the surviving animals were challenged with different strains of each and normal testicular emulsion. It should be noted that in this study all of the challenge strains were heterologous to the infecting strains. The results of this study indicated that there was a substantial degree of cross-protection among the three species of treponemes; also, that there was less cross-immunity between the two syphilis and *cuniculi* strains than between the two heterologous strains of syphilis treponemes and, further, good cross-protection between the two yaws and syphilis strains and less cross-protection between the yaws and *cuniculi* strains.

In the second experiment of Turner and Hollander (1957), nineteen rabbits were infected with *cuniculi* strain A, and a similar group with strain B, and fifteen normal rabbits were used as controls. After 6 months of immunizing infection, challenge was made by injecting approximately 5,000 organisms at six sites on the rabbits' backs. The challenge strains were Nichols and C. J. 39 syphilis strains, yaws strain YD, and *cuniculi* strain A. It was found that the two *cuniculi* strains provided some degree of protection against infection with syphilis strains, but the degree of cross-protection was not as great as one would expect to occur with most syphilis strains. The authors felt justified in concluding that the

two *cuniculi* strains studied differed somewhat in antigenic structure from the two syphilis strains studied.

In another experiment of Turner and Hollander (1957), ten rabbits were infected by the testicular route, allowed to have immunizing infections of 4 months, and challenged by intracutaneous injections of the homologous syphilis strain (Nichols) and with yaws strain YA. This study demonstrated good cross-protection against the homologous strain of syphilis but incomplete protection against the YA strain of yaws treponemes.

In the fourth experiment of Turner and Hollander (1957), a group of rabbits was infected intratesticularly with *cuniculi* strain A and a similar group with syphilis strain C.J. 39. After 8 months of immunizing infection, the infected animals and controls were challenged with 500 Nichols organisms at each of four sites on the rabbits' backs. This study demonstrated complete protection between the two syphilis strains but only partial protection between *cuniculi* strain A and the Nichols strain.

The overall conclusion arrived at by Turner and Hollander (1957) was that their experiments provided ample evidence that there were demonstrable degrees of cross-immunity among all the treponemal strains tested.

Turner and Hollander (1957) have also reported on cross-immunity studies with two groups of syphilis strains. In the first group were nineteen strains that were isolated in either Baltimore or Jamaica. In these studies, either the Nichols strain, *Treponema pallidum*, was used for the immunizing infection and challenge made with one of the several syphilis strains, or the immunizing infection of the several strains was studied in relation to challenge with the Nichols strain. In some instances, both methods were employed with the same strains. The results of their considerable experimentation led Turner and Hollander (1957) to postulate on the antigenic relationships as follows:

With two strains, there was insufficient data; three strains differed from the Nichols strain, but gave some degree of protection (prolonged incubation periods and smaller lesions); fourteen strains appeared to be antigenically identical with the Nichols strains.

It was very unfortunate that most of the nineteen strains were lost after these initial studies, and it was therefore impossible to secure more data on their antigenic relationships.

Turner and Hollander (1957), as a consequence of their relationship with the International Treponematosis Laboratory Centre, were afforded the opportunity of investigating the antigenic relationships of sixteen newly-isolated treponemal strains. The new strains studied were four strains of syphilis, five strains of yaws, three strains of bejel, two strains of

endemic syphilis, and two strains of dichuchwa. In these studies, the Nichols strain was used as the "standard" strain for evoking immunity in rabbits, challenge being made with one of the newly-isolated strains. The immunizing infection with the Nichols strain was made, in each instance, by intratesticular inoculation followed by 3 to 4 months of infection and challenge with 5,000 treponemes at each of four sites on the shaved backs of the rabbits. Control rabbits received the same dose of the same suspension, and test animals found to be negative were observed for 4 weeks after the appearance of lesions in the controls. It was found that the Nichols strain provided a high degree of cross-immunity to all of the new strains that were isolated from patients with venereally-acquired syphilis. The Nichols strain did not provide protection against the yaws strains as a group to the degree found with the syphilis strains, but there was some evidence of cross-protection as evidenced by prolongation of incubation periods and smaller lesions with the yaws-challenged animals. Less cross-protection was also found with the bejel strains. In contrast to the moderate protection against challenge of the yaws and bejel strains, it was found that there was a high order of immunity against the two endemic syphilis strains and the two dichuchwa strains. In a general summation of their data, Turner and Hollander (1957) recognized that the small numbers involved in their studies might have resulted in a high sampling error. Nevertheless, it was their impression that, when the data were examined in relation to groups, the yaws strains as a group and the bejel strains as a group showed significantly lower degrees of cross-immunity with the standard Nichols strain than that observed with the syphilis strains, the endemic syphilis strains, and the dichuchwa strains.

Medina (1964) has summarized his clinical observations spanning $12\frac{1}{2}$ years, during which time five strains of T. pertenue, maintained by monthly passage to healthy humans, were injected into a total of 515 patients infected with T. pallidum, T. carateum, or T. pertenue, and 233 normal human controls. Also 28 pinta patients were studied. Some of the treated pinta cases developed yaws lesions upon challenge with T. pertenue, but "attempts to inoculate untreated pinta patients in the early or late stages with T. pertenue were unsuccessful". Seventy yaws patients (5 had secondary eruptions; 36 were diagnosed late stage, "5—45 years of disease", untreated; and 29 as late stage, previously treated) were challenged with T. pertenue. It was concluded that "yaws patients after the secondary stage, whether treated or untreated, were completely resistant to fresh infection with T. pertenue". The

duration of the infections before treatment of the 29 patients previously treated for yaws was not given nor was the number of organisms of the challenge inocula. A group of 133 syphilis patients which "included most stages of the disease" were challenged with T. pertenue: "in only one of these subjects was the result of the inoculation positive (chancre in serologic stage); the rest were all negative". Inoculation of T. pertenue into 215 syphilis patients previously treated with 6 to 10 million units of penicillin (PAM) resulted in 41 positive inoculations of 148 previously treated for acquired syphilis ("most of them treated in the early phase"), seventeen of 63 "late congenitals", and three of four "early congenitals" developed lesions. Medina was apparently more concerned with the diagnostic aspects of challenge with T. pertenue than with immunological aspects and included a group of children and adults in which inoculation of T. pertenue was used as a diagnostic procedure. The final conclusion of his paper stated, "Inoculation with T. pertenue—a sensitive and safe test—constitutes a valuable aid to the elucidation of obscure cases of yaws, pinta, or syphilis".

It will be recalled that Hudson (1946, 1958) has hypothesized that there are not several treponemal diseases but rather a single disease entity manifested in different ways. The data of cross-immunity studies thus far reported may be interpreted, depending upon one's inclination, to either substantiate or refute Hudson's hypothesis.

MECHANISM OF IMMUNITY

The immunological mechanisms involved in the development of acquired immunity in experimental syphilis have not been determined. Some investigators have been inclined to assign a major role to circulating antibodies and others consider cellular or "tissue" immunity to be predominantly responsible for resistance to reinfection. Still others feel that protection is the result of several immune mechanisms that are interrelated. At this point in our knowledge, the only thing that can be said with any degree of certainty is that there are no unequivocal data which can be cited to defend adequately any particular point of view or hypothesis.

There have apparently been relatively few studies pertaining to the role of cellular immunity in syphilis. A relatively early study was that of Strempel and Armuzzi (1927), in which virulent, treponeme-rich testicular tissue was implanted, subscrotally, into previously-infected but untreated rabbits and into normal control rabbits. It was found, by means of silver stains, that the treponemes of the implants made into previously-infected but untreated animals

were fixed at the implantation site and very slowly disappeared. In contrast to this, the normal animals did not fix the organisms at the implantation site and these were fairly rapidly diffused into the surrounding tissues. A study similar to this, and with similar conclusions, was made by Tani and Aikawa (1940), which differed only in that in the latter study the animals were treated with neo-arsphenamine before making the tissue implantations.

Reynolds (1941) objected to studies such as those of Strempel and Armuzzi (1927) and of Tani and Aikawa (1940) on the grounds that the demonstration of treponemes by means of silver stains is capricious and of questionable reliability, and further, that cicatricial tissues resulting from the immunizing orchitis may have occluded lymphatic channels and possibly prevented the spread of the organisms into the surrounding tissues. In an effort to circumvent these criticisms, Reynolds (1941) developed immunizing infections in a group of rabbits and made implants of testicular tissue infected with the homologous strain into the thighs of the immune rabbits and a control group of normal rabbits. The fate of the organisms in the implants was determined by dark-field examinations, and by transfer of implant tissues and of inguinal lymph nodes into normal rabbits. It was found that the organisms in the implants in normal animals remained motile for 14 days, whereas the organisms in the implants in the immune animals remained motile for only 4 days, and that the treponemes in the implants in the normal animals rapidly migrated to the regional lymphatics in contrast to the immune animals in which treponemes were never demonstrated in lymph nodes by means of node transfer to normal rabbits. Reynolds concluded that the immune rabbit was capable of localizing organisms of the homologous strain at the site of inoculation which were ultimately destroyed by the immune mechanisms of the host. It may be of interest to the proponents of the humoural theory of immunity in syphilis that Reynolds theorized that the disappearance of the organisms from the implantations resulted from local antigen-antibody reaction as the immune antibodies were gradually, but constantly, in contact with the invading organisms.

It appears most likely that reagin bears little relationship to the immune process. Moore (1947) has pointed out that patients may be re-infected while their reagin tests are still positive, and there are many instances of "ping-pong" syphilis in which re-infections have occurred while serological tests for syphilis were still positive. Eagle (1932) produced large amounts of reagin experimentally in rabbits which did not protect the animals on subsequent challenge.

Agglutinins for virulent treponemes were demonstrated by Tani (1940) by the use of suspensions of treponemes obtained by elution from syphilitic testicular tissue. The suspension was stabilized against spontaneous agglutination by the addition of 0·5 to 0·7 per cent. formaldehyde. Serum from normal rabbits and from animals with trypanosomiasis or relapsing fever did not show agglutination, whereas definite agglutination occurred with syphilitic rabbit sera. Further studies on agglutination were made by McLeod and Magnuson (1953a), McLeod and Stokes (1955), and Hardy and Nell (1955). Those studies modified the technique of Tani in certain respects and demonstrated that reagin as well as another antibody (agglutinin) were involved in the agglutination phenomenon *in vitro*. The relationship of agglutinins to immunity in syphilis is not well understood. Turner and Hollander (1957) have found that there is a correlation between immunity and levels of immobilizing and agglutinating antibodies. Rabbits with low levels of both antibodies had low levels of immunity, and a greater degree of immunity was associated with higher levels of both antibodies. Wassermann antibody was included in the studies, and it was found that there was no correlation between the levels of reagin and levels of immunity.

Tani and Aikawa (1936) reported a completely *in vivo* demonstration of circulating antibodies which had an effect on the clinical course of syphilis. Ninety-one pairs of adult male rabbits were parabiosed* for periods of 1 to 34 days, (average 12·8). When pairings were made with one animal with late syphilis and one with a chancre, healing of the chancre was observed if the pairing was successful for 10 days or more. The authors reported that, in some instances, the passively transferred treponemicidal substances were so great that large chancres were healed in short periods of time. It would be of interest to know what effects this continuous means (whole blood) of transfer of antibodies would have on the establishment and maintenance of immunity if performed with animals with adequately-treated late syphilis and normal rabbits.

Kemp and Fitzgerald (1938) studied the passive transfer of protective antibodies in young rabbits born to syphilitic females in comparison with young rabbits born to normal females. There was no appreciable difference in their susceptibility to infection. Of 28 offspring of syphilitic females, 85·7 per cent. were infected, and of 29 offspring of

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* The term parabiosis is used for a technique in which incisions are made into the skin of two animals which are then sutured together so that they come to have a common circulation and anti-bodies pass from one to the other.

normal females, 82·8 per cent. were infected. Magnuson (1948), commenting on this report, suggested that a low degree of immunity might have been present in these animals which was masked by the relatively large challenge inocula used by the authors. In retrospect, particularly in regard to the views of Turner on the relationship of immobilizing antibodies to immunity, it would have been of interest if the immobilizing antibody titres had been known with these rabbits before challenge. Immobilizing antibodies are known to be passively transferred from mother to foetus in human syphilis (Miller, Slatkin, Brodey, Wechsler, and Hill, 1954).

Eberson (1921) reported the demonstration of protective antibodies in the serum of a mother and child. The mother gave no history of infection or treatment. The child was 18 months old at the time protective antibodies were demonstrated and, according to Eberson, was apparently healthy and free from syphilis.

Turner (1939), in much the same manner as Eberson (1921), was able to demonstrate specific humoral antibodies in syphilis by the combined *in vivo* and *in vitro* systems. Briefly, the technique was as follows:

Virulent treponemes were mixed with serum from either normal or syphilitic animals, incubated for a short period, and injected intracutaneously into the backs of normal rabbits. Typical primary lesions developed in most instances at the site of inoculation of normal serum-treponeme mixtures, while at the site of the immune serum-treponeme mixtures, either a lesion did not develop at all or the lesions had a longer incubation period and remained smaller than those produced by normal serum-treponeme mixtures.

Nakano (1913) was apparently the first to demonstrate Pfeiffer's phenomenon with immune serum and cultured treponemes by injecting such mixtures into normal rabbits. The observations of Nakano were not confirmed until 42 years later, when Tani, Matsubara, and Hayashi (1955) reported that mixtures of virulent treponemes and immune serum injected intraperitoneally into guinea-pigs resulted first in the immobilization of the treponemes and the total disappearance of organisms in less than 24 hours. The observations of Tani, Matsubara, and Hayashi were confirmed and extended in two papers by Vaisman and Hamelin (1959, 1960).

Thus, it is obvious that in syphilis there are antibodies of the same nature as those found in other infectious diseases. However, at this point in our knowledge, it is not clear what role or effects any one antibody, or several antibodies combined, play in the establishment and the maintenance of immunity in syphilis. It will be recalled that Turner and Hollander (1957) thought that the levels of immobilizing and agglutinating antibodies correlated in their experimental observations with levels of immunity. Magnuson, Thompson, and McLeod (1951), and McLeod and Magnuson (1953b) also studied the relationship of immobilizing antibodies to resistance with results that were divergent from those of Turner and Hollander. In reviewing the reports of Magnuson, Thompson, and McLeod and of McLeod and Magnuson, Turner and Hollander noted that the titres of immobilizing antibodies of those reports were substantially lower than those of their animals which exhibited a high degree of immunity.

ARTIFICIAL IMMUNIZATION

Many investigators have tried over the years to produce artificial immunity in laboratory animals by the use of killed virulent treponemes and with live and killed cultivable strains of purported *Treponema pallidum*. There are surely many more unsuccessful attempts in addition to those reported in the literature, since most negative investigations are unreported.

Gelperin (1951) thought he obtained a limited degree of immunity in rabbits which he immunized with relatively large numbers of the Reiter treponeme in an adjuvant mixture. A statistical analysis of his observation revealed that there was no significant difference in levels of immunity in his variously-immunized animals and controls. An unreported study in the Venereal Disease Research Laboratory found that no demonstrable immunity resulted from the injection of 200 times the numbers of living organisms reported by Gelperin. In that study, 25 ml. living whole-culture of organisms were injected intraperitoneally twice weekly for 3 months. Upon challenge, the immunized and control animals developed dark-field-positive lesions on the 16th post-inoculation day. Challenge was made intradermally with 1,000 virulent organisms (Nichols strain *T. pallidum*).

Many investigators think that the cultivable strains of purported *Treponema pallidum* were never virulent treponemes but commensals which were admixed with virulent *Treponema pallidum* when originally isolated. Views of this nature can be partially validated by the fact that there are several saprophytic strains of treponemes that have been described from superficial tissues of the genitalia after isolation. However, it is difficult to reason in this manner in regard to the cultivable Nichols strains of *Treponema pallidum*, since Kast and Kolmer (1933) isolated the organisms from a testicular

infection with the virulent Nichols strain. In the unreported study mentioned above, it was also found that 4·8 trillion organisms of the Nichols cultivable strain did not provide any more protection to challenge than did the Reiter strain when both strains were employed during the same 3 months' immunizing period.

To eliminate the problem of strain differences and the question of the origin of the cultivable strains, certain investigators have used the Nichols virulent strain for immunizing and for subsequent challenge. Eagle and Fleischman (1948) did a rather extensive study in which virulent Nichols treponemes were killed with heat, merthiolate, or by maintaining the organisms in the frozen state long enough to destroy their viability. Injections were made intradermally, intraperitoneally, intramuscularly, and intravenously for periods as long as 4 months and with as many as 38 billion organisms. In some series the organisms were suspended in saline, in water and oil adjuvant, and in water and oil with killed tubercle bacilli. Upon challenge with small doses of treponemes (Nichols) there was no clear evidence of increased resistance in any of the several groups of rabbits immunized by different routes and with different total numbers of organisms injected.

Similar studies were reported by Waring and Fleming (1951) and Magnuson, Halbert, and Rosenau (1947), in which lyophilized organisms or testicular syphilomata were emulsified in a Freund-type adjuvant and administered subcutaneously and intramuscularly. In both studies approximately one billion organisms were injected during the immunizing periods. In the study by Magnuson, Halbert, and Rosenau (1947), none of the eighteen animals immunized with lyophilized organisms without adjuvant and none of the nineteen immunized with lyophilized organisms with adjuvant showed any evidence of increased resistance. However, Waring and Fleming (1951) thought that their animals developed some degree of enhanced resistance. Challenge with 200 treponemes of the Nichols strain resulted in dark-field-positive lesions in the test animals, but it was observed that the lesions in the test animals were significantly smaller than those of the controls.

Tani, Inoue, and Asano (1951) treated treponemes with antiformin before use in immunizing schedules. They thought that antiformin was capable of removing surface substances which permitted antigenic substances deeper in the body of the treponeme to become antigenically active. The authors used large numbers of treponemes with each animal (3 to 8 billion) over an immunizing period of 6 weeks. Of 24 rabbits immunized in this

manner and challenged with homologous treponemes, ten did not develop lesions, five developed modified reactions, and nine developed lesions the same as the control rabbits.

IMMUNITY IN HUMANS

Immunity in humans has been the subject of much speculation, influenced by efforts to correlate experimental syphilis in animals with syphilis in humans and by attempts to interpret clinical observations in relation to immunity. There is no doubt that the development of a primary lesion in humans results in an immunity sufficient to prevent the occurrence of a subsequent chancre unless challenged with very large numbers of virulent organisms. There is, however, a possibility of superinfection in late syphilis. The work of Prigge and Rutkowski (1929) demonstrated that under certain conditions asymptomatic superinfections can be established in late syphilis. The authors found that a lesion did not develop when a patient with syphilis of many years' duration was inoculated with a heterologous strain of *Treponema pallidum*, but that an inguinal node inoculation into rabbits was negative before the challenge inoculation and positive afterwards. The problems that clinicians face in the differentiation of "serological relapse", which may be the result of exacerbation of an inadequately-treated infection, from asymptomatic re-infection has been discussed by Chesney and Kemp (1926) and Magnuson (1948). Chesney and Kemp reported that animals developing asymptomatic re-infections demonstrated a serological relapse. Magnuson also found this to be true, providing the animals had experienced a short immunizing infection. Animals with longer immunizing infections did not show serological relapse upon experimental re-infection. These, and other observations, make it apparent that it is not possible, at this time, to employ immunological considerations in the differentiation of an increase in serological titre caused by relapse of an inadequately-treated infection from one caused by superinfection. It is obvious that, in evaluation of experimental treatment schedules in which serological relapses are observed, it is almost impossible to assign given instances to be the result of inadequate treatment, to re-infection, or to superinfection.

The problem of heterologous immunity in syphilis is of only theoretical interest at this time but, if a practical method of actively immunizing against syphilis is developed, the problem would then be real. The report of Eberson (1921), though it contains few observations, is of interest in relation to heterologous strain immunity. Eberson in his studies employed three strains which he had isolated

from a chancre, a lymph node of a patient with latent syphilis, and the semen of a patient with latent syphilis. Using all three of the strains in his protection test with given late syphilitic patients, Eberson found no difference in the protective property of the sera for any special organism. It was his conclusion that, when spirochaeticidal activity was present, all of the strains failed to infect, irrespective of their origin.

Magnuson and others (1956) have made the most recent and the most significant contribution to the problem of resistance to re-infection in relation to diagnostic categories, virulence of the Nichols strain of virulent organisms after approximately 50 years of transfer from rabbit to rabbit, and a determination of the 50 per cent. infectious inoculum in rabbit and man.

There has been some question among workers in this field concerning the degree of infectiousness of the Nichols strain for man after approximately 50 years of transfer from rabbit to rabbit, although instances of accidental laboratory infection have been known to occur. Magnuson and his co-workers found the 50 per cent. infectious inoculum in eight nonsyphilitic human volunteers, inoculated in four sites with graded doses of organisms, to be approximately 57 organisms. The same suspension inoculated into normal rabbits resulted in a 50 per cent. infectious inoculum of 23 organisms. It was thus demonstrated that the Nichols strain has maintained a high degree of infectiousness for man and that the susceptibility of infection with this strain of treponemes is essentially the same for rabbits and man.

An interesting and unexpected observation in the study by Magnuson and others (1956) was the response to challenge between seventeen patients receiving 50 million heat-killed organisms before challenge and of thirty patients who did not receive intradermal or subcutaneous injection of killed treponemes before challenge. Five of the seventeen patients (29 per cent.) who received killed antigen were infected, while 23 of thirty patients (77 per cent.) not receiving the antigen were infected. The difference was found to be statistically significant (P = 0·001). An analysis of the data was attempted in relation to the number of years elapsing since treatment. The average in the group receiving killed organisms was 8·8 years; that in the other group was 10·8 years. That difference was found to be not statistically significant. It should be pointed out that the data were analysed in relation to years since first treatment and that the durations of the immunizing infections before treatment were apparently indeterminate. It would have been of interest, indeed, if the duration of the immunizing infection

before treatment as well as the years since the first treatment could have been evaluated in this study. Regardless of whether killed antigen was or was not injected before challenge, there appeared to be suggestive evidence that the longer the period after treatment, the greater the probability of re-infection, though the evidence was by no means conclusive.

Magnuson and others (1956) reported on a total of 52 human volunteers who had had previous syphilis. All were inoculated intracutaneously with 100,000 virulent (Nichols) organisms at a single site. It may be of importance, in considering the result of this challenge in the various diagnostic categories listed below, that the challenge inoculum was a rather severe one, since it was 2,000 times the 50 per cent. infectious inoculum. The diagnostic categories, the number in each category, and the outcome of challenge was reported as follows:

(1) *Untreated Latent Syphilis (five patients)*.—There was no clinical or serological response to the challenge and all were presumed to have been resistant to super-infection.

(2) *Previously-treated Proved or Presumed Early Syphilis (eleven patients)*.—Nine developed dark-field-positive lesions and two had dark-field-negative lesions. All responded with increased serological titres and were considered to have been re-infected. It was noted that this group developed increases in reagin and immobilizing titres much more rapidly than did the nonsyphilitic controls.

(3) *Treated for Proved or Presumed Re-infection (three patients)*.—One developed a dark-field-positive lesion and one a dark-field-negative lesion. Both had increased serological titres. The third patient showed neither clinical nor significant serological response to challenge.

(4) *Previously Treated for Proved or Presumed Late Latent Syphilis (26 patients)*.—Ten were considered to have been re-infected. One developed a dark-field-positive lesion and nine developed dark-field negative lesions. All ten were found to have increased serological titres. One of the dark-field-negative lesions was considered to be a gumma. Three patients who developed dark-field-negative lesions did not have increases in serological titres. Thirteen patients showed neither clinical nor serological evidence of re-infection.

(5) *Previously-treated Proved or Presumed Congenital Syphilis (five patients)*.—one developed a dark-field-positive lesion, and three developed dark-field-negative lesions with increases in serological titre. One of the dark-field-negative lesions was considered to be a gumma. One patient showed no clinical or serological evidence of re-infection.

(6) *Previously-treated Asymptomatic Central Nervous System Syphilis (two patients)*.—The findings were not conclusive, but one patient may have developed a central

nervous system re-infection and the other showed no evidence of re-infection.

SUMMARY

It is obvious from the many conflicting reports and interpretations of experimental data that there is no unanimity of opinion concerning the development of immunity in syphilis. There are those who follow the concept of Neisser (1911), in which clinically apparent immunity exists only as long as the latent infection persists. Contrasted with this is the concept of Chesney (1927), in which true, but relative, immunity develops which is related to the duration of the original or immunizing infection before termination by adequate therapy. The weight of present experimental data favours the concepts of Chesney (1927).

There seems to be no doubt that the persistence of infection results in humoural and tissue changes which can only be interpreted as resistance of the host against the parasite. Experimental data which have demonstrated the presence of humoural factors are the studies of Eberson (1921) and of Turner (1939), and perhaps the parabiosing experiments of Tani and Aikawa (1936), and the demonstration of Pfeiffer's phenomenon by Nakano (1913), Tani, Matsubara, and Hayashi (1955) ,and Vaisman and Hamelin (1959). Altered tissue response was demonstrated by Reynolds and others, in experiments in which implanted treponemes remained *in situ* in presumably immune animals and were systemically disseminated in non-immune animals.

Numerous experiments have demonstrated relative resistance to re-infection in rabbits which have been correlated with the duration of the original infection; however, there have been few experiments concerned with the duration of resistance after adequate therapy. It is not known if an antigenic focus must be maintained for resistance to be held at a certain level and, thus, the concepts of Neisser (1911) have not been conclusively refuted. The interesting studies of Collart and co-workers (1962a, b, c) on the persistence of treponemes in late syphilis after presumably adequate treatment, if coupled with degree and duration of immunity, could conceivably contribute significantly to our knowledge of immunity in syphilis as well as the effectiveness of particular treatment methods in late syphilis.

There are many recognized, and probably unrecognized, technical difficulties to overcome before sufficient numbers of virulent organisms can be made available for the studies that will be necessary to gain further insight into the mechanisms of immunity in syphilis. Assuming that subsequent research will provide a practical technical methodology to produce immunity, there will be the problem of developing and evaluating a successful immunization programme. One can assume that the social stigma associated with the disease itself would persist in public attitude toward immunization against it. It would therefore seem unlikely that mass immunization programmes such as those employed against poliomyelitis would be successful. Perhaps it is not important at this time for public health administrators to be concerned with the practical employment of a vaccine against syphilis, but it would be well to be aware of social and moral problems that could be expected to arise that have never arisen in the practical application of vaccination against any other disease.

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Immunité dans la syphilis

RÉSUMÉ

Il est évident d'après les nombreux exposés et interprétations d'expériences contradictoires que les avis ne sont pas unanimes en ce qui concerne le développement de l'immunité contre la syphilis. Il y a ceux qui sont d'accord avec le concept de Neisser (1911), d'après lequel une immunité clinique apparente existe seulement autant que l'infection persiste. Par contraste le concept de Chesney (1927) affirme qu'une immunité reélle mais relative se développe, et que celle-ci est proportionnelle à la durée de l'infection immunisante originale avant sa termination par une thérapie adéquate. Le poids des travaux expérimentaux actuels fait peser la balance en faveur des concepts de Chesney (1927).

Il semble qu'il n'y ait aucun doute que les changements humoraux et tissulaires sont le résultat de l'infection prolongée et peuvent être interprétés seulement comme résistance de l'hôte contre le parasite. Les travaux qui ont prouvé la présence de facteurs humoraux sont les études d'Eberson (1921) et de Turner (1939) et peut-être les expériences de parabioses de Tani et Aikawa (1936), et la mise en évidence du phénomène de Pfeiffer par Nakano (1913), Tani, Matsubara, et Hayashi (1955) et Vaisman et Hamelin (1959). Reynolds et ses collègues ont mis en évidence des réactions tissulaires modifiées, par des expériences où les tréponèmes implantés restaient localisés chez des animaux immunisés mais étaient systématiquement disséminés chez des animaux non immunisés.

De nombreuses expériences faites chez les lapins ont demontré une résistance relative à la réinfection proportionnelle à la durée de l'infection originale; cependant il y a eu peu de travaux sur la durée de la résistance au tréponème après une thérapie adéquate. On ne sait pas s'il faut maintenir un foyer d'antigènes pour que la résistance de l'organisme atteigne un certain niveau, et ainsi les concepts de Neisser (1911) ne sont pas définitive-

ment réfutés. Les études intéressantes de Collart et ses collègues (1926a, b, c) sur la persistance des tréponèmes dans la syphilis tardive après traitement adéquat pourraient, si elles s'accompagnaient d'une étude de la degré et la durée de l'immunité, augmenter de façon considérable notre connaissance de l'immunité dans la syphilis ainsi que celle de l'efficacité de certaines méthodes de traitement dans la syphilis tardive.

Il y a beaucoup de difficultés techniques connues et inconnues à surmonter avant qu'un nombre suffisant de microbes virulents puissent être disponibles pour les études nécessaires qui permettraient d'approfondir les mécanismes de l'immunité dans la syphilis. En admettant que les recherches à venir fourniront une méthodologie technique pratique pour produire une immunité, il reste encore le problème de développer un programme d'immunisation efficace. On peut prévoir que le stigmat social associé à la maladie persisterait envers l'immunisation. Il semble peu probable qu'un programme d'immunisation en masse semblable à celui institué pour la poliomyélite aura du succès. Peut-être est il prématuré que les administrateurs du service de la santé publique se préoccupent de l'application pratique d'un vaccin contre la syphilis, mais il faut prendre conscience des problèmes moraux et sociaux qui se poseront et qui ne se sont jamais posés au sujet des autres vaccins.